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Pilot Study of Ambient Air Pollution and Survival from Cancer

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Research Triangle Park, NC

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January 1980

PILOT STUDY OF AMBIENT AIR POLLUTION AND SURVIVAL FROM CANCER

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

This report presents the results of a pilot study concerned with investigating the possible association between the length of survival of diagnosed cancer patients and ambient levels of particulates and sulfur dioxide characterizing their area of residence. Previous studies have shown increased mortality among elderly and chronically ill populations during air pollution disasters. There has also been increasing evidence of a possible influence exerted by air pollution upon cancer incidence and mortality. However, the influence that exposure to air pollutants may have upon the survival time of a severely stressed and especially susceptible population, such as diagnosed cancer patients, has yet to be evaluated. The results of this preliminary study suggest that high levels of ambient air pollution may adversely affect the health of certain types of cancer patients. Additional research of this nature is clearly warranted.

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ABSTRACT

This study was concerned with investigating the potential influence exerted by ambient concentrations of particulate and sulfur dioxide air pollutants upon the length of survival for diagnosed cancer patients. Monitoring data from the National Aerometric Data Bank for particulates and sulfur dioxide were examined in conjunction with survival data from the Lakes Area Regional Tumor Service Registry. Length of survival for respiratory cancer patients was found to be inversely related to maximum particulate levels. Survival times for patients who resided in areas where maximum particulate levels exceeded 240 $\mu g/m^3$ were significantly shorter than for similar patients who resided in areas with lower particulate levels. Colorectal cancer patients demonstrated a similar trend that was not statistically significant. No association was found between survival of leukemia patients and particulate or SO_2 levels, nor was SO_2 related to survival of respiratory tract or colorectal cancer patients. These findings suggest that highly polluted air in residential areas may have a deleterious effect on the survival time of patients with certain types of neoplastic disease. Additional research is called for of the relationship between cancer survival and exposure to ambient air pollution, especially particulates.

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Gerald Nehls, Statistics and Data Management Office, Health Effects Research Laboratory, U.S. Environmental Protection Agency, contributed greatly to the study effort by obtaining and providing air quality data from the SAROAD system. Deborah Lorshbough aided in data entry activities involving both the Lakes Area Regional Tumor Service Registry and the SAROAD information.

SECTION 1. INTRODUCTION

It has been recognized for many years that air pollution may have untoward consequences for human health. This concern has been reinforced by the health effects that have been observed pursuant to the occurrences of several major air pollution disasters. For instance, in 1930, a large number of residents in the Meuse Valley, Belgium, became severly ill after the Valley was blanketed for three days by a combination of industrial smoke and fog. Approximately sixty deaths from heart failure, mostly among the elderly and chronically ill, were attributed to this episode. Sulfur oxides and fluorine may have been the major culprits (1). More recent episodes that are thought to have had serious health consequences have occurred in Donora, Pennsylvania (2), London (3), Los Angeles and Piscataway, New Jersey (4).

During the past decade, considerable attention has been directed toward potential environmental precursors of malignant neoplasms. Evidence of an environmental effect has come from several sources. Studies of migrants have shown their rates for several types of cancer to vary from those of their former homeland to those of their adopted country, and among succeeding generations (5,6,7). Several reports have demonstrated considerable variation in cancer incidence or mortality rates between industrialized and less developed countries (8,9). Within the United States, differences in county cancer mortality rates have also been shown (10). In addition, several studies have shown a tendency of rates for many types of cancers in urban areas to exceed rates in rural areas (11).

The contribution of exposure to air pollutants in the ambient air to the etiology of most cancers has yet to be demonstrated for most cancer sites. The effects of occupational exposures to such substances as asbestos, dust in uranium mines, vinyl chloride, and beta naphthylmine are well known. The urban excess for lung cancers as well as the results of several studies showing excess rates among residents of heavily polluted urban neighborhoods suggests that air pollution may exert a significant etiologic effect (12).

Most considerations of a potential air pollution effect for neoplasms are concerned with an etiological influence. However, if we review the findings of studies concerned with the health consequences of air pollution disasters, we find that major effects occur mainly among the elderly and those suffering from a chronic illness. This suggests that rather than concentrating only upon the etiologic significance of air pollutants, it may be worthwhile to investigate health effects among those individuals who are already severely stressed (13).

No investigations have yet been conducted of the possible influence of ambient air pollution levels upon the survival time of individuals who have been diagnosed and undergone treatment for cancer. Based upon the previously mentioned findings, it would appear that such individuals would comprise a population highly susceptible to contaminants in the ambient air. Approximately one-third of those who contract cancer survive for five years or more after being diagnosed. Furthermore, the treatments employed often carry such side effects as depressed immunity and decreased resistance to infection. These factors suggest that many

cancer patients residing in heavily polluted areas may be more highly susceptible to systemic infections, respiratory problems and other complications than are similar patients who reside in less polluted regions. If true, this would result in decreased survival times for patients from highly polluted areas, especially those with respiratory involvement such as lung cancer patients, or those with depressed immunity as a result of treatment such as leukemia patients.

SECTION 2. CONCLUSION

The analyses performed in this pilot study revealed a significant association between length of survival from diagnosis for respiratory cancer patients and high maximum particulate levels characterizing area of residence. No significant effects for levels of particulates or sulfur dioxide upon survival were found for leukemia or colorectal cancer patients. However, the relationship of maximum particulate levels to the survival of these patients, although not statistically significant, was in the same direction as that of survival among respiratory cancer patients.

Since the methods employed in this pilot study to measure exposure to air pollution were crude, it is not surprising that more significant results were not found. Many assumptions were required and knowledge of the ambient pollutant levels under which cancer patients live is, at best, approximate. The results that were obtained indicate that more precise measurements may yield clear-cut detrimental influences of air pollution upon cancer survival after diagnosis and treatment.

These findings imply that exposure to very high levels of particulates may prove harmful to patients with respiratory cancer as indicated by decreased survival times. The same may hold true for similar patients who are exposed to very high levels of sulfur dioxide and for colorectal patients exposed to high levels of these same pollutants. However, because of the crude manner in which exposure was measured in this pilot study, we may only conclude that such a possibility may exist and that additional research is clearly warranted.

SECTION 3. RECOMMENDATIONS

Since this pilot study was a limited effort and primarily an assessment of feasibility, recommendations will be constrained to suggestions for future research.

A large number of assumptions were necessary in order to obtain estimates of effluent levels representative of the environment in which a cancer patient resided. For example, it must be assumed that mean values of ambient pollution levels in the zip code area that included both the monitoring station and the patient's residence were representative of the exposures experienced by the patient after diagnosis and treatment of his condition. Fortunately, the precision of these estimates can be improved in several ways. First, annual isopleth maps for particulates and sulfur dioxide, as well as other pollutants, should be used to provide a more precise measure of mean and maximum levels in the immediate area of a given residence. Second, the residence of each cancer patient needs to be more accurately located than is possible by zip code alone. Paper records of patient residence addresses are available from the Lakes Area Regional Tumor Service Registry and will be used in conjunction with a follow-up effort. Third, variables that may affect survival such as stage of disease, tumor grade, type of treatment as well as socioeconomic status should be included in future analyses. In the present study, a lack of reliable information on some of these factors as well as further erosion of the amount of cases available for analysis precluded their inclusion.

Improved accuracy in evaluating the correlation of pollution to survival can be obtained by plotting patient residences on an accurate contaminant isopleth map. In addition, since no cases would be eliminated for lack of a pollutant reading in the zip code area where the patient resided on the year of diagnosis, more Registry cases would be available for analysis. If the above recommendations were adopted, the patient sample sizes would double.

Although the findings of this pilot study do not allow definitive conclusions or recommendations regarding the association between pollutant levels and survival to be made, they do suggest that further examination of this problem is desirable. The additional expense and effort that is necessary to achieve an acceptable degree of accuracy does seem warranted on the basis of these preliminary findings. Thus, the primary recommendation is to conduct additional investigations of this potential problem.

SECTION 4. MATERIALS AND METHODS

The purpose of this pilot study was to assess the influence that air pollution may exert upon the survival of diagnosed cancer patients. It was hypothesized that length of survival would be inversely associated with levels of air pollutants. Survival among respiratory cancer patients would be affected because of involvement of the respiratory system. Leukemia patients were selected because of the depressed immunity they experience as a result of treatment. Colorectal patients were chosen as a comparison group. Such patients do not have the direct involvement of the respiratory tract as do lung cancer patients, and they do not experience depressed immunity from therapeutic procedures to the same extent as do leukemia patients.

Data Preparation

Data from the Lakes Area Regional Tumor Service Registry were combined with pollution levels from the National Aerometric Data Bank to produce information sets for various cancer sites. Site by site analyses were then performed to determine the relationship between ambient pollutant levels and survival from date of diagnosis.

The Lakes Area Regional Tumor Service Registry contains data on approximately 26,000 cancer patients who were treated at hospitals located in western New York and northern Pennsylvania. The Registry master file contains various elements of demographic data as well as treatment summary and follow-up information. For this study, residence zip code, diagnosis date, site of histology (ACS Red Book codes), date of last follow-up and patient status were the main parameters extracted from the master file.

The National Aerometric Data Bank contains mean and maximum readings for various sampler sites scattered about the catchment area of the Lakes Area Registry. The pollutants sampled and the years in which sampling was conducted varies widely between sampler locations. While particulates were generally sampled, the years in which sampling actually took place were somewhat variable. A visual inspection indicates that sulfur dioxide was the only other pollutant recorded consistently enough to allow meaningful determination of its affect on survival.

The first step of the analysis was to determine the zip code zone in which the various samplers are located. It was then possible to construct data files containing records of sampler site, zip code, and mean and maximum pollutant levels for the years 1970 through 1976. The files were then sorted by zip code, and average values for maximum and mean ambient concentrations were computed by year within each zip code. This process was repeated for particulates and sulfur dioxide.

Next a computer program was written to collate the pertinent information on each patient in the Lakes Area Registry with the average pollutant level in the residence zip area during the year of diagnosis. Cases were eliminated who were diagnosed before 1970, had a residence zip code outside of western New York, had no pollutant sample values in their zip code area for the year of diagnosis, or contained an obvious data error. The total number of cases and the number available for analysis by pollutant are given for the initial sites of interest in Table 1.

TABLE 1. CASES AVAILABLE FOR ANALYSIS BY TYPE OF POLLUTANT

Site	Total Cases	Cases Available for Analysis: Particulate Matter	Cases Available for Analysis: SO_2
Leukemia (ACS Red Book Histology) Code 9800-9949	577	315	154
Respiratory (ACS Red Book Site) Code 1600-1639	2622	1463	774
Colorectal (ACS Red Book Site) Code 1530-1539	3163	1687	865

The reduced number of evaluable cases under sulfur dioxide is due to the smaller number of sampler recordings for that pollutant.

Cox Modeling

A series of Cox Modeling analyses were then performed on the various data sets. Cox Modeling is a multivariate nonlinear regression technique designed to accommodate censored data in the analysis of survival. The technique allows the assessment of the effect of multiple covariates on hazard function and, thus, survival under the assumption of exponential failures (14).

Life Tables

Life table analyses were conducted using mean and maximum particulate levels to form exposure groups. Breslow tests were completed in order to determine the significance of the difference in survival distributions between the two groups (15).

SECTION 5. RESULTS AND DISCUSSION

Average mean and maximum levels of particulate matter for the years 1970 thru 1976 were categorized for the zip codes corresponding to the sampler locations. Tables 2 and 3 present these data.

Several observations are worth discussion. First, it is obvious that considerably more data regarding particulates are available than for sulfur dioxide. This has a direct bearing on the types of analyses that may be conducted. Also, the range of variation tends to be much greater for maximum particulate levels than for mean levels by both sampler location and year of measurement.

A problem that immediately surfaces concerns depletion of the number of patients available for analysis due to a lack of or inconsistency of monitoring data. Regarding particulate matter, this problem is especially observable for data collected during the early seventies. On the other hand, the number of stations measuring sulfur dioxide levels was much less than the number measuring particulate matter.

Initially, a series of univariate regression analyses were conducted to determine the relationship between pollutant level and risk of death. As demonstrated by Table 4, the risk of death among leukemia and colorectal patients is not significantly associated with either mean or maximum particulate levels, nor mean or maximum levels of sulfur dioxide. However, for respiratory cancer patients, the risk is significantly associated with maximum particulate levels.

TABLE 2. AVERAGES* OF MEAN AND MAXIMUM PARTICULATE COUNTS BY ZIP CODE

Zip Code	1970		1971		1972		1973		1974		1975		1976	
	Mean	Max	Mean	Max	Mean	Max	Mean	Max	Mean	Max	Mean	Max	Mean	Max
14006					38	106	39	114	44	180	47	120	40	110
14011					26	31	46	114	31	72	40	97	36	110
14020			67	136	58	122	53	138	45	110	47	98	36	65
14031									47	122	48	132	44	141
14043									58	155	58	140	54	156
14048	58	131	63	134	64	128	67	177	58	134	60	132	49	143
14063														
14070														
14072									46	85	49	115		
14080	42	91	53	386	38	94	41	124	34	72	45	110	36	119
14086			50	95	51	117	53	179	48	111	49	128	48	158
14092	74	188	84	222	85	192	81	209	68	167	68	175	55	139
14094	59	141	70	197	64	137	69	235	57	126	59	141	50	150
14101	45	94	48	106	45	131	45	128	38	115	45	109	39	103
14105	53	140	57	144	51	111	56	168	47	96	57	147	46	132
14120	117	263	121	254	82	152	74	159	64	124	63	143	56	155
14131													44	127
14132	59	117	57	135	53	109	50	122	47	119	54	113	45	121
14136					42	65	57	139	76	718	55	102	52	141
14150	95	199	105	296	82	159	72	142	91	151	113	286	115	345
14174											56	114	49	148
14203			103	222	95	237	87	296	94	266	82	201	60	151
14206	134	462	134	333	117	292	112	279	99	259	74	189	99	281
14207					70	128	74	120	72	136	74	156	68	157
14210	181	592	152	385	137	363	136	309	136	312	103	243	110	253
14211	82	156	79	187	76	135	79	204	61	108	60	122	60	137
14212	97	250	93	211	78	146	75	145	70	128	63	128	61	172
14213														
14214	76	144	87	357	72	139	65	141	62	108	55	110	48	134
14215									74	157	79	202	60	154
14216			94	323	81	182								
14217			92	202	87	155	73	134	69	129	69	130	56	127
14218	162	425	126	321	117	275	126	371	134	385	137	379	111	289
14219			75	150	78	282	68	151	64	174	71	153	68	234
14220			86	177	102	279	104	351	94	236	96	239	91	414
14221									70	145	84	223		
14224			67	146	76	254	65	139	73	201	66	142	59	177
14225	100	210	88	304	92	214	72	163	75	212	71	158	72	177
14226			72	140	74	133	70	160	69	148	75	219	63	155
14263														
14301			111	313	108	226	101	251	96	224	99	196	75	191
14302	118	259	110	249	104	174	101	241	83	153	75	154	64	140
14303			107	215	103	222	71	95						
14304	215	512	128	307	109	230	96	272	85	195	93	201	76	172
14305	111	276	107	227	96	219	93	198	96	293	89	174	63	154
14482														
14569	41	53	62	346	53	166	48	113	42	119	55	116	44	109
14701	75	195	81	201	78	197	75	225	56	172	73	192	48	141
14705					25	46	54	342	39	121	36	92	38	117
14719	42	120	50	114	44	126	30	70	25	68	38	100	36	96
14733			52	121	42	88	44	129	35	91	34	78	39	106
14760	63	293	54	117	56	164	54	139	62	164	48	94	49	104
14772	40	89	45	106	41	95	29	63	24	57	37	82	32	110
14802									23	44	29	67	25	89
14895					27	66	49	108	34	74	40	109	39	102

*Values are $\mu g/m^3$

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TABLE 3. AVERAGES* OF MEAN AND MAXIMUM SULFUR DIOXIDE COUNTS BY ZIP CODE

Zip Code	1970		1971		1972		1973		1974		1975		1976	
	Mean	Max	Mean	Max	Mean	Max	Mean	Max	Mean	Max	Mean	Max	Mean	Max
14006														
14011														
14020														
14031							1	1	1	3	1	4	1	10
14043														
14048														
14063									10	39	11	87	3	12
14070														
14072														
14080														
14086									8	28	5	28	6	32
14092	39	150	29	150	35	196	42	145	19	111	11	51	9	56
14094			14	36	22	73	41	112	24	120	11	42	13	47
14101														
14105							33	49	22	139	11	41	9	31
14120			26	78	30	73	42	87	31	164	13	91	18	80
14131														
14132							54	105	29	172	10	37	11	65
14136														
14150			10	10	4	25	22	60	12	50	14	64	13	70
14174														
14203									14	45	16	48	10	38
14206			40	290	33	480	34	569	28	279	26	234	24	183
14207							10	10						
14210			16	40	8	40	35	80	26	110	32	145	37	157
14211							22	50	12	50	11	45	11	60
14212									14	40	9	30	12	41
14213														
14214									13	50	8	36	11	42
14215														
14216			13	30	2	10								
14217							10	10	11	46	9	44	15	79
14218							24	70	17	42	15	55	21	67
14219														
14220											20	40	19	51
14221														
14224														
14225			10	20	4	30	16	50	14	60	12	42	13	42
14226							24	50	13	60	10	35	10	33
14263														
14301														
14302	38	210	21	143	27	131	30	660	20	220	16	82	12	67
14303														
14304			41	131	50	244	67	164	34	159	19	82	17	74
14305	80	50												
14482														
14569														
14701					7	12	15	94	15	69	11	40	11	38
14706									14	87	11	96	13	100
14719														
14733														
14760									7	23	4	43	4	35
14772														
14802														
14895									3	17	4	42	1	6

*Values are $\mu g/m^3$

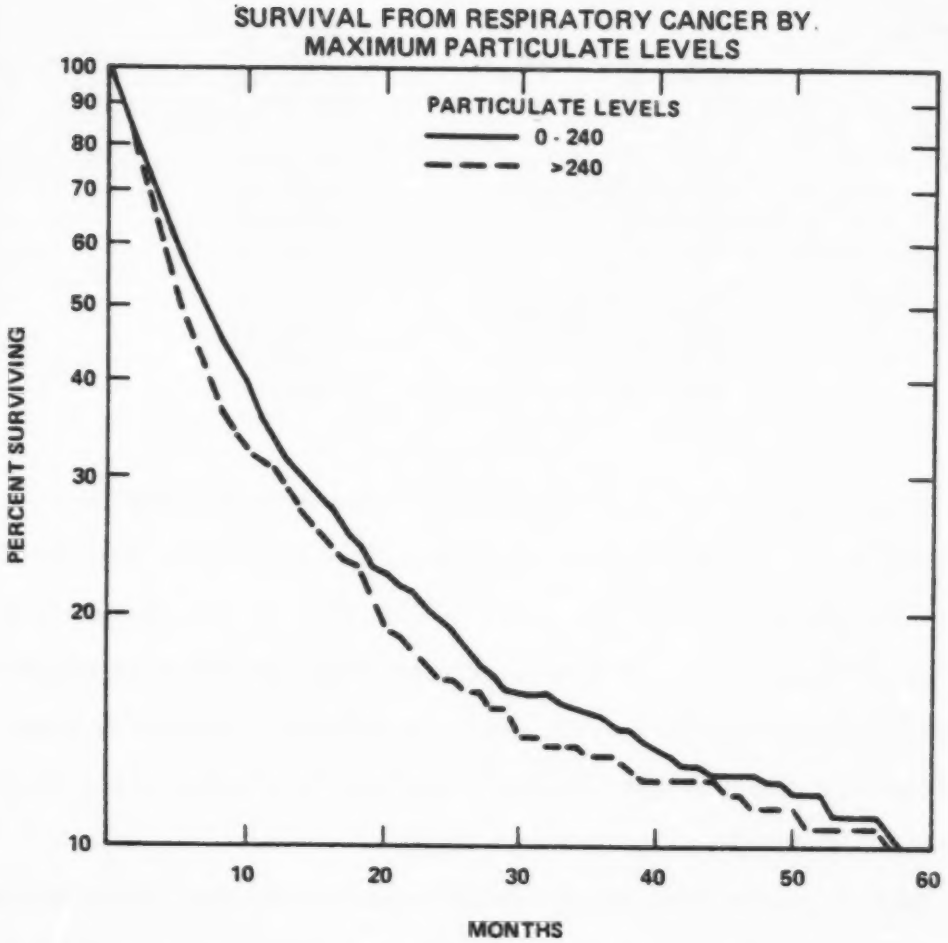
TABLE 4. REGRESSION TABLE FOR CANCER SITE AND TYPE OF POLLUTANT

Site	Covariate	Coefficient of Covariate (βi)	Significance of βi
Leukemia	Mean Particulate	.1328E-02	.61
	Max. Particulate	-.3950E-03	.62
	Mean SO_2	-.9680E-02	.33
	Max. SO_2	.1177E-02	.29
Respiratory	Mean Particulate	.6741E-03	.55
	Max. Particulate	.6671E-03	.05
	Mean SO_2	-.2374E-02	.51
	Max. SO_2	.2982E-03	.48
Colorectal	Mean Particulate	.1491E-02	.25
	Max Particulate	.5859E-03	.17
	Mean SO_2	.5893E-02	.88
	Max. SO_2	.3495E-03	.45

This finding is further supported by Figure 1 which presents an actuarial survival comparison of respiratory cancer patients residing in areas with maximum particulate levels of 240 $\mu g/m^3$ or less versus areas with higher levels. The difference between these two curves is statistically significant at the $\alpha = .05$ level. Individuals residing in areas where maximum levels exceed 240 $\mu g/m^3$ consistently display poorer survival than those residing in less polluted areas.

Table 5 presents in somewhat greater detail the relationship between cancer site, particulate levels and median survival. The only significant difference in survival once again occurs for respiratory tract cancers. Median survival for patients residing in areas characterized by maximum particulate levels less than 240 $\mu g/m^3$ is 7.0 months compared to 5.2 months in higher pollution areas.

Figure 1



BRESLOW TEST RESULTS: $p < .05$

TABLE 5. MEDIAN SURVIVAL BY PARTICULATE LEVELS AND CANCER SITE

Site	Groups	Median Survival	Significance of Difference in Survival Distributions
Leukemia	I - Mean Part. 0-80	15.2 mo.	NS
	II - Mean Part. > 80	17.4 mo.	
Leukemia	I - Max. Part. 0-240	15.9 mo.	NS
	II - Max. Part. > 240	15.1 mo.	
Respiratory	I - Mean Part. 0-80	6.7 mo.	NS
	II - Mean Part. > 80	6.3 mo.	
Respiratory	I - Max. Part. 0-240	7.0 mo.	$p < .05$
	II - Max. Part. > 240	5.2 mo.	
Colorectal	I - Mean Part. 0-80	24.5 mo.	NS
	II - Mean Part. > 80	22.8 mo.	
Colorectal	I - Max. Part. 0-240	24.3 mo.	NS
	II - Max. Part. > 240	22.6 mo.	

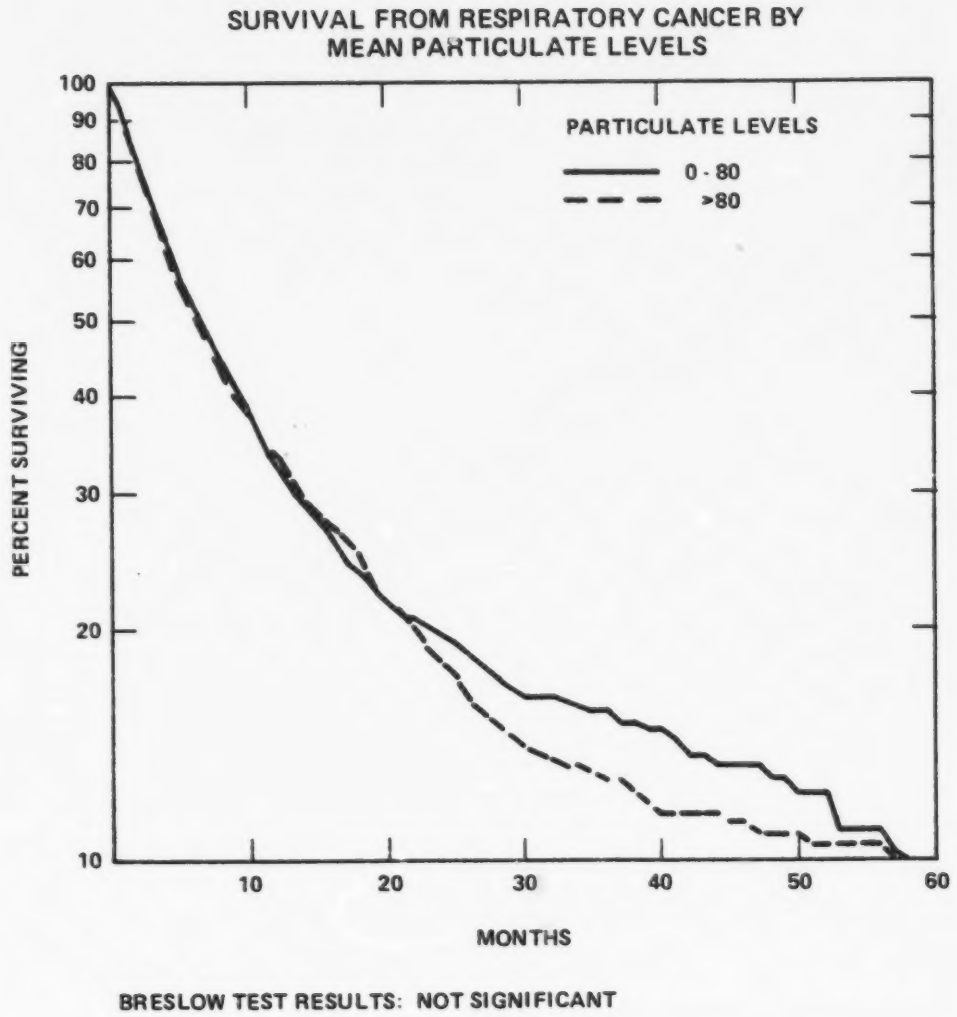
Qualifications

It is important to understand the assumptions underlying the Cox Modeling performed. It must be assumed that the mean value of the ambient concentrations in the zip code area of residence during the year of diagnosis is representative of the conditions under which the cancer patient lived the remainder of his life. This is indeed a considerable supposition. A cursory inspection of the time progression of particulate and SO_2 levels indicates a tendency for the mean reading to decline with time. Also, maximum values demonstrate no consistent trend which may be attributed to sampling being conducted on a periodic schedule such as

every third day rather than daily. This indicates that even if a cancer patient remained at home after being diagnosed, the mean level to which he or she was exposed probably declined.

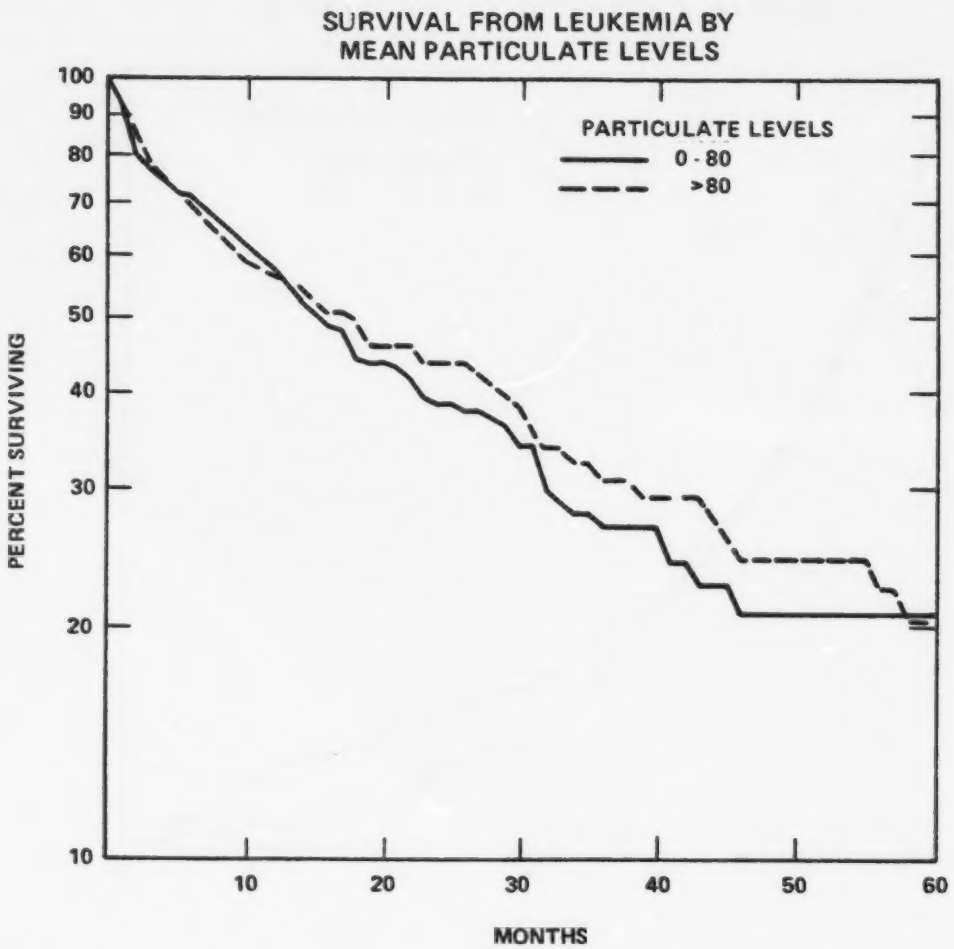
Finally, it should be remembered that this was a pilot study designed to assess, in a preliminary manner, whether the hypothesis that length of survival among diagnosed cancer patients was associated with ambient pollutant levels is worthy of continued investigation. Although the only significant relationship found was between survival of respiratory cancer patients and maximum particulate levels, the same trend was also observed for both colorectal and leukemia patients. Given the crude measures consisting of available data that were employed in this investigation, one might argue that any bias that might exist would be against obtaining significant findings. Thus, it may be concluded that, although definitive statements about a possible association between the length of survival of cancer patients and ambient concentrations of particulate matter are not yet warranted, continued investigation of this potential problem is justified.

Figure 2



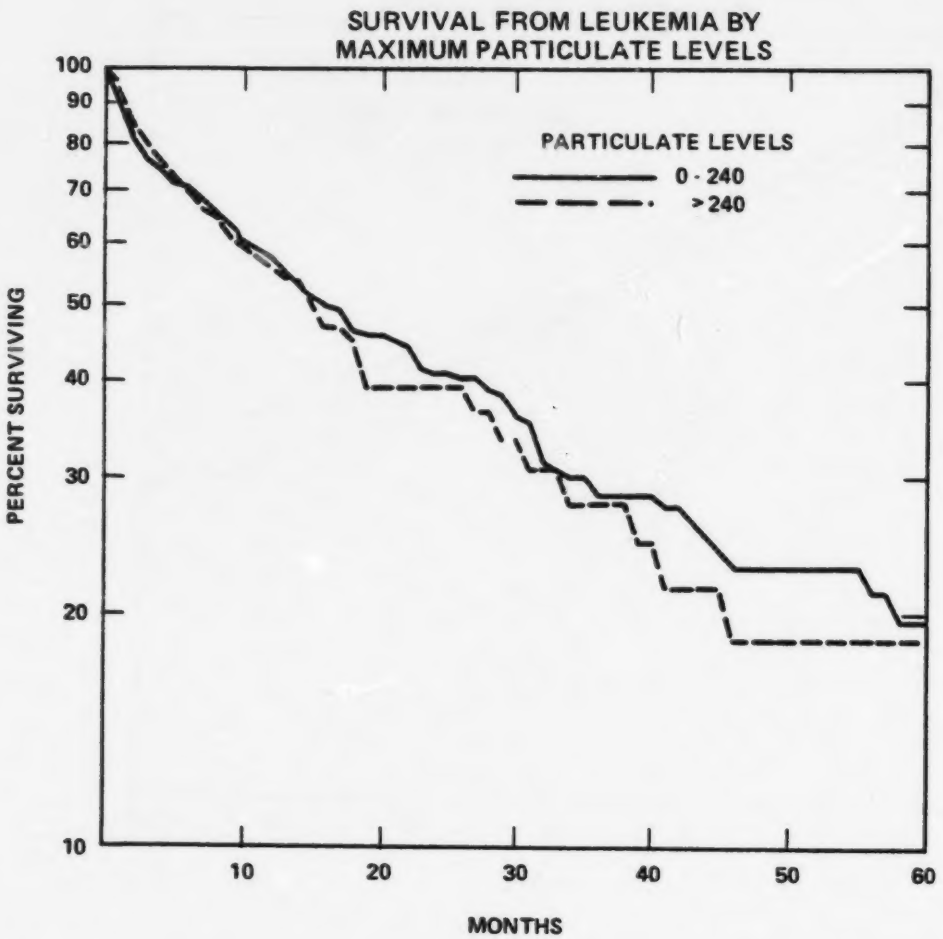
BRESLOW TEST RESULTS: NOT SIGNIFICANT

Figure 3



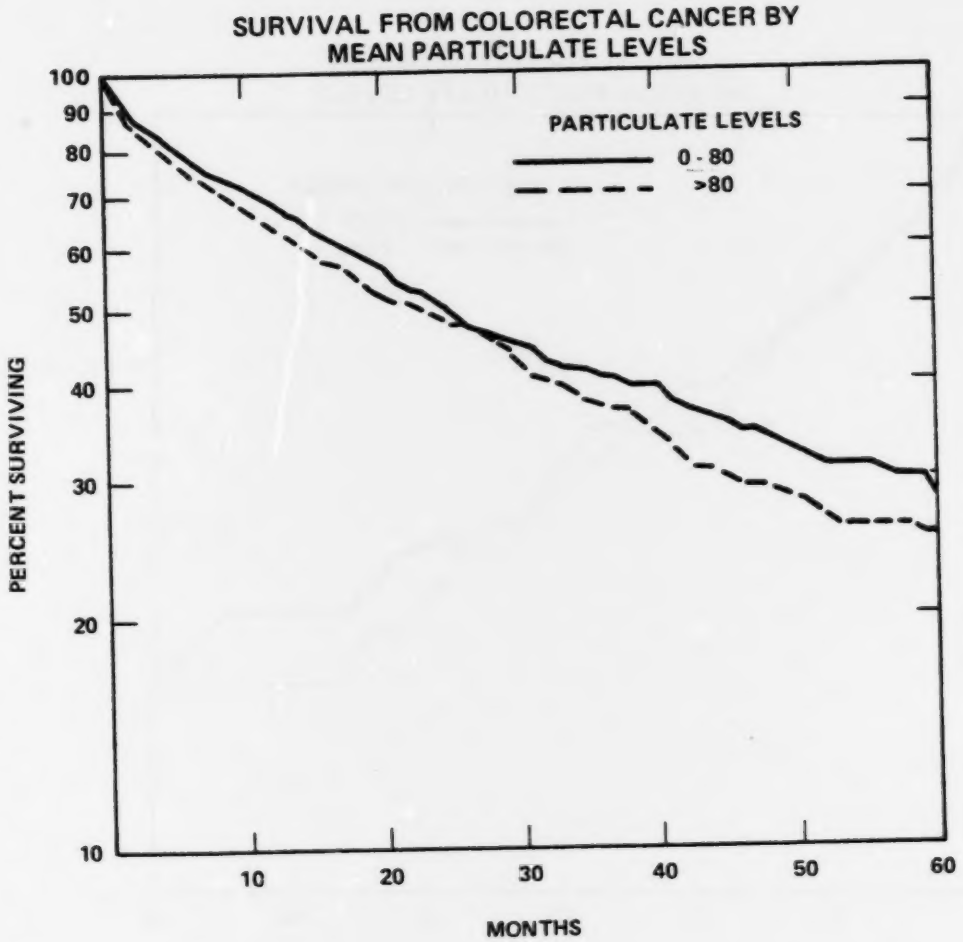
BRESLOW TEST RESULTS: NOT SIGNIFICANT

Figure 4



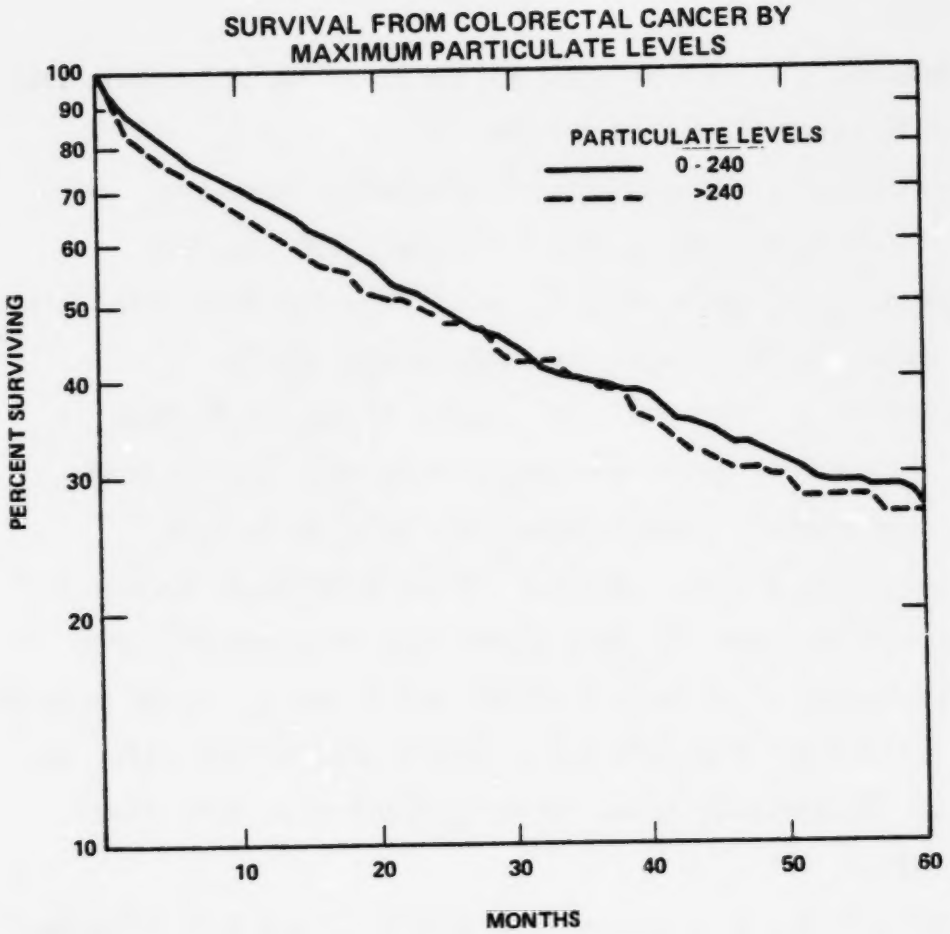
BRESLOW TEST RESULTS: NOT SIGNIFICANT

Figure 5



BRESLOW TEST RESULTS: NOT SIGNIFICANT

Figure 6



BRESLOW TEST RESULTS: NOT SIGNIFICANT

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16. ABSTRACT

This study was concerned with investigating the potential influence exerted by ambient concentrations of particulate and sulfur dioxide air pollutants upon the length of survival for diagnosed cancer patients. Monitoring data from the National Aerometric Data Bank for particulates and sulfur dioxide were examined in conjunction with survival data from the Lakes Area Regional Tumor Service Registry. Length of survival for respiratory cancer patients was found to be inversely related to maximum particulate levels. Median survival for those patients who resided in areas where maximum particulate levels exceeded 240 $\mu g/m^3$ was significantly shorter than for similar patients who resided in areas with lower particulate levels. Colorectal cancer patients demonstrated a similar trend that was not statistically significant. No association was found between survival of leukemia patients and particulate or SO_2 levels, nor was SO_2 related to survival of respiratory tract or colorectal cancer patients. These findings suggest that highly polluted air in residential areas may have a deleterious effect on the survival time of patients with neoplastic disease. Additional research is called for of the relationship between cancer survival and exposure to ambient air pollution, especially particulates.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Sulfur Dioxide Particulates Aerometric Cancer		06,F,P

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